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FUNGAL INFECTIONS IN TRANSPLANTATION (S SHOHAM, SECTION EDITOR)

Fungal Infection and Prevention in Lung Transplant

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Abstract

Purpose of Review We reviewed common fungal infections and prevention in lung transplant. We paid special attention to the impact of diagnostic and pharmacologic advances on preventative and treatment strategies.

Recent Findings Lung transplant recipients receiving anti-mold agents appear to have a survival benefit compared to those not receiving anti-mold agents, but patients may be selected to receive medications by data not captured. Pre-emptive strategies aimed at preventing invasive mold infections may leave lung transplant patients vulnerable to invasive candidiasis in the early post-transplant period.

Summary Lung transplant recipients are susceptible to fungal infections. No uniformly accepted prophylactic strategy exists. While universal prophylaxis with systemic azole agents has gained traction, evidence is limited regarding its efficacy. Pre-emptive strategies for prevention of fungal infections have had mixed success in single-center cohorts and are limited by currently available tests to detect early infection. More studies are needed to determine the optimal preventative strategy.

Keywords Lung transplant · Fungal infection · Immunocompromised · Antifungal prophylaxis

Abbreviations

BAL	Broncho-alveolar Lavage
ECMO	Extracorporeal Membrane Oxygenation
IC	Invasive Candidiasis
IFI	Invasive Fungal Infections
IMI	Invasive Mold Infections
LTR	Lung Transplant Recipients
PCP	Pneumocystis *jirovecii*
PCR	Polymerase Chain Reaction

Introduction

Fungal infections are frequently encountered in solid organ transplant recipients. Candidiasis, mold infections, endemic fungi, and *Pneumocystis jirovecii* can all occur following transplantation, but the risk of infection is dependent upon the type of solid organ transplant, time from transplant surgery, and individual host risk factors. While small bowel and liver transplant recipients are at highest risk for developing invasive candidiasis (IC), lung transplant recipients (LTR) are at highest risk for developing invasive mold infections (IMI) [1]. The risk for invasive fungal infections (IFI) is greatest within the first several months post-transplant, but LTR remain at increased risk for IMI years following transplant surgery for several reasons: (1) the lung allograft remains in constant contact with the environment allowing for inhalation of fungal spores, (2) lung transplant recipients remain on relatively intense pharmacologic immune suppression to prevent and treat allograft rejection, (3) lung transplant surgery impairs cough and mucociliary clearance of inhaled pathogens, and (4) airway and parenchymal anatomic abnormalities predispose to respiratory tract colonization with potential pathogens [2].

Fungal infections, particularly IMI, have been associated with an increase in all-cause mortality in LTR [3]. Secondary to this, most lung transplant centers prescribe antifungal

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medications with the goal of preventing IFI [4•]. Herein, we describe the most common fungal infections encountered in lung transplant, discuss preventative strategies, and address advances in diagnostics and pharmacologic therapies.

Candida Infections

Candida sp. infections generally occur in the post-transplant period secondary to operative or hospital related complications such as surgical site infections or line-related infections. Surgical site infections for LTR include empyema, mediastinitis, sternal osteomyelitis, and soft-tissue incisional infections. While *Candida* sp. infections are the second most common type of fungal infection in LTR, they remain more common in liver and small bowel transplant recipients [1].

Preventing Infection in Lung Transplant

In the USA, most transplant centers utilize universal antifungal prophylaxis for LTR [4•, 5]. Universal prophylaxis means that all LTR receive antifungal medications. Other prophylactic strategies include selective (also known as targeted) prophylaxis where patients with additional risk factors for fungal disease receive antifungal medications, and pre-emptive prophylaxis where patients with colonization or biomarkers indicative of possible early fungal disease receive antifungal medications.

While the goal of universal prophylaxis in LTR is generally to prevent IMI, the most prescribed regimen of triazole with or without nebulized amphotericin [4•] may prevent early post-transplant IC. Other antifungal prophylactic strategies aimed at preventing IMI in LTR, such as selective or pre-emptive regimens, generally do not select for IC risk factors or monitor for pre-emptive initiation of antifungals for possible IC biomarkers and therefore may fail to prevent IC. This concern was recently raised by a retrospective cohort study of LTR that received nebulized liposomal amphotericin and preemptive prophylaxis aimed at preventing IMI [6••]. In this cohort, the prevalence of IC was 11.4% [6••]. All first episodes occurred within 60 days post-transplant leading the authors to conclude that systemic antifungal prophylaxis may be beneficial in the first 90 days following lung transplant to prevent IC. This conclusion has not yet been validated by other centers that utilize selective or pre-emptive prophylactic approaches in LTR.

Selective antifungal prophylaxis if aimed at specifically preventing IC in LTR may be successful. This strategy is commonly used to prevent IC in liver transplant patients. Like lung transplant, IC usually manifests as candidemia or surgical site infections that include intra-abdominal infections [7]. Predisposing risk factors include procedure-related and host factors such as known colonization with *Candida,* acute renal failure, renal replacement therapy, diabetes, antimicrobial therapy pressure, neutropenia, central venous catheter use and parenteral nutrition. For liver transplant recipients, choledochojejunostomy, anastomotic leaks, repeat abdominal surgery and re-transplantation and high transfusion requirement of cellular blood products are among identified surgical factors [8–10]. Use of selective antifungal prophylaxis has been associated with decreased risk of IC in liver transplant, though various duration regimens reported [11]. Despite targeted antifungal prophylaxis, breakthrough IC can be seen in liver transplant with a recent report near 5% in orthotopic liver transplant recipients [12]. The rate of breakthrough infections in LTR on antifungal medications has not been established.

Advances in Diagnostics

Pre-emptive prophylactic approaches aimed at IC rely on accurate diagnostic tools to detect colonization and/or early infection. While diagnostic tools currently in development may be appropriate to use as a basis for pre-emptive prophylaxis, there are currently no sufficient diagnostic tools clinically available. The impact and natural history of *Candida* sp. airway colonization in LTR is unknown and is unlikely to independently be an appropriate marker for initiation of pre-emptive antifungal therapy. Serum *B*-1,3-D glucan detection, commercially known as Fungitell assay, is highly sensitive for IC but lacks specificity [13]. *B*-1,3-D glucan is contained in the cell wall of most fungal organisms and can be falsely elevated in patients receiving blood products including intravenous immunoglobulin and those on renal replacement therapy or cardiopulmonary bypass [14]. T2Candida panel is a newer clinically approved assay that uses a combination of nuclear magnetic resonance and polymerase chain reaction (PCR) to detect *Candida* sp. on whole blood [15, 16]. Further investigations are needed to fully assess the diagnostic accuracy of this assay in LTR; at this time, this assay should not be used in singularity to make decisions regarding pre-emptive therapy or treatment in transplant patients.

Advances in Pharmacologic Therapy

When selecting prophylactic medications, consideration should be given to spectrum of activity, tolerance and side effects, interactions with immune suppression medications, and medication cost as many antifungal medications can be prohibitively expensive for patients. The antifungal drugs active against IC include echinocandins, azoles, and amphotericin B formulations. Any of these medications may prevent IC, but echinocandins and azoles are most used for prophylaxis in transplant patients.

Ibrexafungerp is a novel antifungal drug recently approved for vulvovaginal candidiasis, but its role in invasive disease and in transplant recipients is yet to be demonstrated [17]. In transplant patients with suspected or confirmed candida bloodstream infection, the first line treatment is an echinocandin such as anidulafungin, caspofungin or micafungin [18]. A novel long-acting echinocandin, rezafungin, is currently undergoing clinical trials for candidemia and invasive candidiasis [19]. Susceptibility testing of the *Candida* isolate for azoles and echinocandins is warranted for all bloodstream and other clinically significant *Candida* isolates. Treatment may be transitioned to oral fluconazole among patients who are clinically stable and whose isolates are determined to be susceptible to fluconazole. Among non-critically ill patients without risk factors for drug-resistant candida, fluconazole may be used initially as alternative to an echinocandin.

Candida glabrata and *Candida krusei* are often resistant to fluconazole. For initial treatment of candidemia due to *C. glabrata* and *C. krusei*, an echinocandin is preferred over amphotericin B formulations. *C. krusei* isolates can have diminished susceptibility to amphotericin B, and thus, echinocandin treatment may be continued for the duration of therapy. If susceptible, voriconazole may be used as oral step-down treatment. Echinocandin is also the first line empiric treatment for *Candida auris*, a highly resistant species that has emerged in recent years. Specific targeted therapy should be guided by susceptibility testing.

Lung Transplant Patients with Extra-corporeal Life Support as Bridge to Transplantation

Lung transplant candidates bridged to transplant with veno-venous or veno-arterial extracorporeal membrane oxygenation (ECMO) are a unique subset of patients. While little evidence exists to support routine antifungal prophylaxis with veno-venous ECMO [20], ECMO bridge to transplant does increase the risk of IC in LTR. This subset of patients should receive anti-candida prophylaxis following transplant. Additionally, patients with congenital heart disease requiring veno-arterial ECMO bridge to heart–lung transplant are also at particularly high risk for IC and should receive anti-candida prophylaxis [21].

Candida Superbugs

While pharmacologic prevention strategies for IFI are often the focus in lung transplant, universal prescribing of antifungal medications may not be enough and may contribute to the development of fungal superbugs. Just as other multi-drug resistant pathogens have increased world-wide, there have been numerous reported outbreaks due to *Candida auris* in healthcare settings, known for its drug resistance and potential for outbreaks, including infections in transplant recipients [22, 23]. Limited treatment strategies for the nosocomial organism are further complicated by its propensity to create outbreaks. A mitigation strategy to slow the spready of *C. auris*, has included recommendations to fully identify yeast from sterile sites in the lab, screening strategies on hospital admission to hospitals for those from endemic areas, and utilization of strict infection control strategies and investigation if a case arises [24]. Unfortunately, a recent report noted the presence of echinocandin and pan-resistant cases of *C. auris* in the USA, with 3 infected patients lacking previous antifungal exposure prior to the diagnosis, yet still developed *C. auris* pan-resistant infection, suggesting transmission or resistant organism in the healthcare setting [25].

Invasive Mold Infections

Most fungal infections in LTR are secondary to *Aspergillus* sp. and manifest as tracheobronchitis or pneumonia [26, 27]. Invasive aspergillosis most commonly occurs within the first six months following transplant but can occur any time after transplant [1]. Other organisms causing IMI in LTR include Mucorales, *Fusarium*, and *Scedosporium* [26, 27].

Preventing Infection in Lung Transplant

IMI are a source of high morbidity and mortality in LTR [3]. As evidenced by clinical practice surveys, US lung transplant centers have increasingly turned to pharmacologic antifungal prophylaxis as a strategy to prevent IMI. In a 1999 survey, 76% of US lung transplant centers used antifungal prophylaxis post-transplant [5]. This proportion increased to 97.5% of centers in 2018 [4•]. Furthermore, there has been a dramatic shift toward universal prophylaxis. Only 52% of centers used a universal prophylaxis strategy in 1999; however, by 2018, 90% of centers used universal prophylaxis [4•, 5]. Strategies for prophylaxis beyond universal, selective, or pre-emptive include topical prophylaxis with nebulized amphotericin to prevent airway infections or use of systemic antifungal agents usually with azole agents.

A large study (N = 815) utilizing universal inhaled amphotericin therapy demonstrated a high rate of IFI (19.1%) including both IMI and IC [6••]. Moreover, previous analyses of systemic prophylaxis with itraconazole were associated with a prevalence of IMI of 16.5% [28]. Equipoise regarding clinical benefits of antifungal prophylaxis led to a recent systematic review/meta-analyses which was inconclusive regarding benefit [29]. Subsequently utilizing insurance claims data, the use of systemic anti-mold prophylaxis following lung transplant appeared to have a survival benefit compared to LTR who did not receive prophylaxis

[30••]. However, it is unclear if patients receiving prophylaxis were selected by prescribers for reasons that could not be captured by insurance claims data. Antifungal prophylaxis agents are expensive and sometimes associated with issues of absorption, skin cancer risk, liver enzyme elevation, drug-drug interactions with immunosuppression, and break through infections depending on the agent utilized [31]. In the absence of inexpensive and innocuous prophylactic agents, future researchers should strive to define the optimal prophylactic strategy and duration in the lung transplant population.

Advances in Diagnostics

Pre-emptive prophylaxis against IMI, specifically *Aspergillus* sp., most often utilizes broncho-alveolar lavage (BAL) culture or galactomannan to initiate antifungal medications [6••, 32]. Galactomannan is a cell-wall constituent that is released during replication in *Aspergillus* sp. [33]. While serum galactomannan is not sensitive in solid organ transplant recipients, galactomannan in BAL specimens has a sensitivity of 88% for invasive aspergillosis in solid organ transplant recipients [34].

Aspergillus PCR is a relatively new molecular method for the early diagnosis of invasive aspergillosis. PCR methods have not been standardized, but this diagnostic modality appears to have high specificity in serum samples with modest sensitivity [35] making it unlikely to be a useful adjunct for pre-emptive prophylactic strategies. Aspergillus PCR on BAL samples has high sensitivity [36] and may eventually be utilized to guide pre-emptive prophylaxis; however, Aspergillus PCR has not been studied in solid organ transplant recipients.

Advances in Pharmacologic Therapy

Itraconazole, voriconazole, posaconazole, and isavuconazole are the azole agents with activity against *Aspergillus* sp. Secondary to their oral formulation, they are most often used for systemic prophylaxis against IMI in LTR [4•, 30••].

Voriconazole is currently the antifungal drug of choice for invasive aspergillosis [37]. Posaconazole was found to be non-inferior to voriconazole in terms of all-cause 42-day mortality among patients with invasive aspergillosis [38]. Isavuconazole was also found to be non-inferior to voriconazole in a study of 527 patients with invasive aspergillosis and other mold infections [39]. Echinocandins and an amphotericin B formulation are alternative agents. Combination antifungal therapy has been used in severe disease, and when there is a concern for drug-resistant fungal infection. In addition to antifungal drugs, the intensity of immunosuppression should be reduced, and necrotic tissues should be debrided.

Intravenous administration of lipid formulation of amphotericin B, often at high doses (standard 5 mg/kg daily, or increased dose to 10 mg/kg daily), is the drug of choice for initial therapy of mucormycosis [40]. Amphotericin B treatment is continued until patients have shown clinical improvement. Among the triazoles, posaconazole and isavuconazole may be active in vitro against mucormycosis and are considered alternatives in patients who are unable to tolerate amphotericin B or used as oral step-down regimens in patients who have shown clinical improvement. In a multicenter open-label single-arm study, the clinical outcomes of 37 patients treated with isavuconazole for proven or probable mucormycosis were comparable to control patients who received amphotericin B followed by posaconazole [41]. Early aggressive surgical debridement of necrotic and infected tissue has been associated with improved survival.

Endemic Fungi

LTR that reside in endemic areas may be at increased for infections caused by *Histoplasma capsulatum*, *Blastomyces* sp., and *Coccidiodes immitis*. In general, universal strategies aimed at preventing IMI are also effective against endemic mycoses. Additionally, avoidance of soil and decaying vegetation by LTR may help prevent infection by these pathogens.

Advances in Diagnostics

Beyond pharmacologic prophylaxis, accurate and rapid diagnosis of endemic fungal infection in LTR is vital to early treatment. The diagnosis of IFI can come from variety of available diagnostics, including serologic, antigen testing, histopathology findings, culture results, and infrequently PCR based testing. Although fungal cultures have remained the gold standard, as identification of endemic fungal organisms is always pathogenic, relying on culture results alone would result in delayed diagnosis. Cultures may yield results one to four weeks after collection, and at times require invasive procedures to obtain needed samples. *C. immitis* is the exception, as this organism can grow on routine bacterial cultures, as early as a few days after collection. Similarly, histopathology can be very useful in identifying organisms when using special stains, evaluating for granuloma but is limited by invasive procedures required to obtain tissue samples.

Serologic testing has long been available but remains a concern when evaluating immunosuppressed population due to the possibility of false negative testing. As such, these tests are of limited value in LTR. In addition, serologic testing can be hampered by common cross-reactivity between the endemic fungal organisms. Serologic testing

for coccidiomycosis in immunocompromised hosts however can be helpful, though may need to be repeated if performed earlier in the disease course.

The most utilized and reliable testing for disseminated endemic fungal infections in transplant recipients has transitioned to antigen testing. In a report of histoplasmosis after solid organ transplantation of 152 cases, urine histoplasma antigen was the most sensitive diagnostic method (93%) used [42]. For best performance in histoplasmosis diagnosis, combining antigen testing in serum and urine results in highest sensitivity. Similarly antigen testing in urine and serum when evaluating for blastomycosis has resulted in improved rapidity of establishing a diagnosis, as compared to conventional culture and histopathology.

Antigen testing yields a rapid turnaround as compared to cultures and improved sensitivity as compared to serologic testing, is noninvasive and can be helpful for monitoring patient treatment response or evaluation for relapse of disease. The largest pitfall in antigen testing is the loss in specificity, as cross reactivity between endemic fungal organisms can be seen [43].

Molecular testing, including nucleic acid detection direct from specimen can help in direct tissue and culture specimens, but the role of these tests in clinical practice has not been established.

Advances in Treatment

The approach to treatment of endemic fungi in LTR as with other populations depends on clinical severity and site of infection [44]. Amphotericin B and azoles are the backbone for antifungal treatment, while echinocandins are generally ineffective for the dimorphic endemic mycoses.

Itraconazole, fluconazole, voriconazole, posaconazole, isavuconazole and amphotericin B have activity against *H. capsulatum*. Among these drugs, itraconazole is preferred for mild to moderate histoplasmosis, and amphotericin B is recommended for the treatment of moderately severe and severe histoplasmosis. Oral itraconazole therapy is recommended for continuation of therapy in patients who were initially treated with amphotericin B.

Treatment of transplant patients with coccidioidomycosis includes fluconazole as the preferred drug over itraconazole because of its limited gastrointestinal absorption [45]. Amphotericin B is reserved for patients with severe coccidioidomycosis and those with life-threatening complications [44]. Patients treated with amphotericin B are transitioned to fluconazole or itraconazole upon improvement in clinical status. Antifungal therapy should be continued indefinitely because transplant patients remain on long-term immunosuppressive therapy. The intensity of immunosuppressive drug regimen should be reduced, if possible.

Treatment of blastomycosis includes amphotericin B or one of the azole drugs, most often itraconazole [44, 46]. Mild to moderate pulmonary blastomycosis may be treated with itraconazole. Lipid formulation of amphotericin B is the drug of choice for initial therapy in patients with moderately severe to severe pulmonary blastomycosis, and those with disseminated disease. Once clinical improvement is achieved, the treatment can be switched to itraconazole. Voriconazole, posaconazole and fluconazole may be used as alternatives in patients who are unable to tolerate itraconazole. Relapses are common in patients with continued immunosuppression, and long-term itraconazole suppressive therapy is generally recommended.

Pneumocystis Jirovecii

Lifelong prophylaxis against *Pneumocystis jirovecii* (PJP) is often utilized in LTR due to the high prevalence and associated morbidity without prophylaxis [47]. The risk of PJP following transplant is eight times higher in the first twelve months than in subsequent years in non-lung transplant recipients [48]. Whereas other solid organ transplant programs may not utilize life-long prophylaxis, six to twelve months is recommended [49]. Certain risks factors for PJP infection should prompt consideration of reinitiation of PJP prophylaxis in transplant recipients: increased corticosteroids or other immunosuppression in the presence of graft rejection, CMV or BK-related infections, neutropenia or lymphopenia, HLA mismatch, or use of rituximab or lymphocyte-depleting therapies [49, 50].

Prophylaxis is often completed with trimethoprim-sulfamethoxazole. Alternatives for patients who are intolerant of trimethoprim-sulfamethoxazole are atovaquone or dapsone. Inhaled pentamidine should be avoided as a solo agent for the prevention of PJP in LTR. Some experts would advocate for de-sensitization prior to transplantation in sulfa allergic patients to allow for trimethoprim-sulfamethoxazole, but this is not a uniformly accepted practice.

Conclusion

LTR are susceptible to fungal infections, most commonly IC and invasive aspergillosis. Aside from universal lifelong prophylaxis against PJP, no uniformly accepted prophylactic strategy against IFI in LTR exists. While universal prophylaxis with systemic azole agents has gained traction in the United States in recent years, evidence is limited regarding its efficacy. Targeted or selective antifungal prophylactic strategies have demonstrated efficacy in other solid organ transplant recipient groups, such as liver transplant recipients, and may be effective in LTR if appropriate risk factors

for IC and IMI can be identified. Pre-emptive strategies for IMI have had mixed success in single-center cohorts. Newer diagnostic tests and antifungal agents may help treat LTR with IFI when prophylaxis fails. At present, however, mortality associated with IFI in LTR remains high. More research is needed to inform clinical practice to determine if pharmacologic prophylaxis can be effective in preventing IFI in LTR.

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Conflict of Interest Dr. Razonable received research grants from Roche, Regeneron, Gilead and is a DSMB member of Novartis. The remaining authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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